



JUL 25 2003

WARNING LETTER

VIA FEDERAL EXPRESS

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

I. Howard Fine, M.D.
1550 Oak Street, Suite 5
Eugene, OR 97401

Dear Dr. Fine:

This letter informs you of objectionable findings noted during a Food and Drug Administration (FDA) inspection conducted at your clinical site and acknowledges your April 18, 2003, letter to Mr. Charles Breen, Director, Seattle District Office (SEA-DO). Ms. Lori Silverstein and Mr. Robert Tollefsen, investigators from the FDA's SEA-DO conducted the inspection from March 31 to April 4, 2003. The purpose of the inspection was to determine if your activities as a clinical investigator in the [REDACTED] study sponsored by [REDACTED] complied with applicable FDA regulations. The [REDACTED] is a device as that term is defined in Section 201 (h) of the Federal Food, Drug, and Cosmetic Act (the Act).

The FDA conducted the inspection under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval Applications (PMA), and Premarket Notification (510(k)) submissions are scientifically valid and accurate. Another program objective is to ensure that human subjects are protected from undue hazard or risk during scientific investigations.

Our review of the inspection report prepared by the district office revealed serious violations of Title 21 Code of Federal Regulations (21 CFR), Part 812-Investigational Device Exemptions, Part 50-Protection of Human Subjects, and Section 520(g) of the Act. You received a Form FDA 483 "Inspectional Observations" at the conclusion of the inspection that listed the deviations noted and discussed with you and others. The deviations noted on the Form FDA 483, our subsequent review of the inspection report, and your response to the FDA 483 items are discussed below:

Failure to adhere to the general and specific responsibilities of a clinical investigator [21 CFR 812.100 and 812.110(a) and (b)]

You submitted the current version of [REDACTED]
[REDACTED]
[REDACTED], " to the IRB concurrently with a request for sub-investigator approval. Your records showed that the IRB approved the sub-investigators in April 2000, but did not specifically approve the revised protocol which included a protocol name change, protocol amendments, and revised informed consent documents.

Accordingly, you conducted research on human subjects without continuous IRB approval. Although you attributed these omissions to IRB oversights and inadequate communication with the IRB, as a clinical investigator you are responsible for maintaining IRB approval and relevant documentation throughout the study. We note that you obtained IRB approval for the revised protocol, amendments, and informed consent documents on April 7, 2003.

Failure to maintain accurate, complete, and current subject records [21 CFR 812.140(a)(3)].

There were discrepancies between the information recorded in source documents and the data recorded on case report forms (CRFs). Several examples of these discrepancies follow:

- The visual acuity reading for subject eye [REDACTED] is not recorded on the CRF and is incorrectly recorded for subject eye [REDACTED]
- Technicians performing subjects' evaluations only initialed the front pages of the relevant source documents rather than signing and dating the completed source documents. These documents also contained crossed out data without dates or initials indicating who corrected the forms or when the corrections were made.
- Comparisons of the CRFs and the Data Line Listings submitted by the sponsor showed discrepancies regarding five subject eyes [REDACTED]
- An adverse event case form for subject eye [REDACTED] was erroneously completed and removed from the subject's file at the sponsor's direction. Although the protocol defined cystoid macular edema as a pathological condition/complication rather than an adverse event, the form should have remained as part of the patient's file to document all complications associated with the device.

Failure to maintain device accountability records [812.140(a)(2)]

The device accountability records you supplied during the inspection were incomplete. Many of the receipt records lacked signatures/dates and contained improperly documented changes. The return records consisted of photocopies containing obscured data and did not include the reasons for returning the lenses.

The deviations listed above are not intended to be an all-inclusive list of deficiencies that may exist at your facility. As a clinical investigator, you are responsible for ensuring that you conduct clinical trials according to FDA regulations.

Your response indicates that you have developed some corrective measures and plans to ensure that these deviations are not repeated in the future. Your corrective measures should also include plans, and sufficient staff, to audit the study data; procedures to assure that you have IRB approval and documentation of protocols, amendments, and

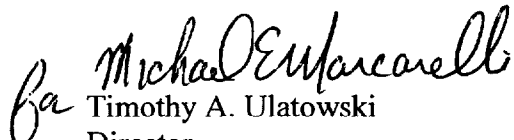
Page 3-I. Howard Fine, M.D.

informed consent documents; methods to assure device accountability; and procedures to assure that patients' records are complete and accurate.

Please advise this office, in writing, within fifteen (15) working days after receiving this letter of the additional, specific steps you have taken to correct these violations and prevent the recurrence of similar violations. Include any documentation necessary to show that the corrective actions have been achieved. Failure to respond may result in the FDA taking regulatory action without further notice to you. Please direct your response to the following address: Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch II (HFZ-312), 2098 Gaither Road, Rockville, Maryland 20850, Attention: Sybil Wellstood, Ph.D.

We are also sending a copy of this letter to FDA's Denver District Office and request that you also send a copy of your response to that office. If you have any questions, please contact Dr. Wellstood by phone at (301) 594-4723, ext. 140, or by email at saw@cdrh.fda.gov.

Sincerely yours,


Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health